

REMARKS

Claims 1-18 are pending in the application. Claims 4, 5, and 11-18 are under examination. Claims 1-3 and 6-10 are withdrawn in response to the prior restriction requirement. In the Office Action mailed November 19, 2007, claims 4 and 5 are objected to because of an informality. Claims 5, 11-15, and 18 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Claims 5, 11-13, 15, 16, and 18 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. Claims 4 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pat. App. Pub. No. 2003/0171325 (Gascoyne et al., hereinafter "Gascoyne"). Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gascoyne in view of U.S. Pat. No. 7,062,385 (White et al., hereinafter "White").

I. Claim Objections

Claims 4 and 5 are objected to because of an informality, the recitation of "newly synthesized nucleic acid" instead of "synthesized nucleic acid". The Specification is objected to because the drawing numbers are not correctly referred to in the Brief Description of the Drawings. The Applicants have herein amended claims 4 and 5 to delete all uses of "newly". The Applicants have also amended dependent claims 12, 14, 15, 17, and 18 in the same manner. No new matter is added by these amendments. Entry of these amendments and withdrawal of the objections claims 4 and 5 is therefore respectfully requested.

II. Rejections under 35 U.S.C. 112, first paragraph

Claims 5, 11-15, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, claims 5 and 14 are rejected because the specification allegedly fails to define or provide any disclosure to support the claim limitation "based on results from the step of monitoring, detecting errors in the sequence of the newly synthesized nucleic acid" because the specification "does not describe that [sic], based on results from the step of monitoring, detecting any kind of errors such as insertion errors in the sequence of the newly synthesized nucleic acid." Also, claims 12 and 15 are rejected because the cited passages of the specification, Figures, and originally filed claim 6 allegedly fail to define or provide any disclosure to support the claim

limitation “detecting a change in electrophoretic force exerted by the newly synthesized nucleic acid as it grows.”

As a preliminary matter, the Applicants note that, while claims 11, 13, and 18 are stated as being rejected under this section, no explanation of the reason for rejection of these claims is given. Although it is not stated, the Applicants presume that claims 11, 13, and 18 are rejected for being dependent on claim 5. The Applicants have in this response made this assumption; however, clarification of the reasons for rejection of claims 11, 13, and 18 under this section, or withdrawal of the rejections, is respectfully requested.

The Applicants respectfully traverse the rejections of claims 5 and 14. In order to more particularly point out and claim the invention, the Applicants have herein amended claims 5 and 14 to recite the step of eliminating deletion errors in the sequence of the synthesized nucleic acid. These amendments clarify that the errors detected and eliminated by the method of claims 5 and 14 are deletion errors. Support for these amendments is found in the Specification at least at paragraphs [0030] and [0136], and in Fig. 14B. No new matter is added by these amendments. Entry of the amendments and withdrawal of the rejections of claims 5 and 14, as amended, is therefore respectfully requested.

The Applicants respectfully traverse the rejections of claims 12 and 15, and respectfully disagree that the specification, Figures, and originally filed claim 6 allegedly fail to define or provide any disclosure to support the claim limitation “detecting a change in electrophoretic force exerted by the newly synthesized nucleic acid as it grows.” The limitation recited in claims 12 and 15 relates to the use of a specific device, known as a “magnetic (or optical) tweezer.” Such a device is well-known in the art, and is discussed in many of the references disclosed by the Applicants in the Information Disclosure Statement submitted in this case, including, but not limited to, ASSI, Fabiano et al., “Massively parallel adhesion and reactivity measurements using simple and inexpensive magnetic tweezers“, *J. Appl. Phys.*, Vol. 92, No. 9, 5584-5586 (1 Nov. 2002); GOSSE, Charlie et al. “Magnetic tweezers: micromanipulation and force measurement at the molecular level“, *Biophysical Journal*, Vol. 82, 3314-3329 (June 2002); HABER, Charbel et al., “Magnetic tweezers for DNA micromanipulation“, *Rev. Sci. Instrum.*, Vol. 71, No. 12, 4561-4570 (Dec. 2000); and HOSU, Basarab G. et al., “Magnetic tweezers for intracellular applications“, *Rev. Sci. Instrum.*, Vol. 74, No. 9, 4158-4163 (Sept. 2003).

Furthermore, the limitation of claims 12 and 15 is clearly disclosed in paragraphs [0022] and [0119] of the Specification, which state, in part: “The support is held in a fixed equilibrium position by applying an electric field and magnetic field gradient created by the magnetic tweezers that opposes the electrophoretic force. ... Assuming the zeta-potential of the dielectric bead is constant, *the addition of an oligonucleotide strand is the only contribution to the increase in electrophoretic force felt by the particle.* The increased electrophoretic force moves the bead from its equilibrium position, and the magnetic field gradient must be increased to restore the bead to its equilibrium position. *Optically determined bead velocity and restoration force correspond to the number of bases added.* Therefore, the length of the added strand can be ensured to be correct.” (emphasis added). A suitable apparatus is depicted in Figs. 15F and G, and described in paragraph [0143], while the results from an actual experimental run of a reduction to practice of the methodology claimed is depicted in Figs. 15A-E and described in paragraphs [0137] – [0142]. The Applicants therefore respectfully maintain that the limitation of claims 12 and 15 is fully supported by the written description, that it is clear that the inventors, at the time the application was filed, had possession of the claimed invention, that the underlying technology of the limitation is well-known in the art of the invention, and that the rejected claims therefore satisfy the requirements of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejections of claims 12 and 15 under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

III. Rejections under 35 U.S.C. 112, second paragraph

Claims 5, 11-13, 15, 16, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. As a preliminary matter, the Applicants note that, while claims 11, 15, and 18 are stated as being rejected under this section, no explanation of the reason for rejection of these claims is given. The Applicants have in this response made the assumption that claim 15 is rejected for the same reason as claim 12, with which it shares a limitation. However, it is unclear why claims 11 and 18 have been rejected, and so no response to the rejection of them can be made. Clarification of the reasons for rejection of claims 11, 15, and 18 under this section, or withdrawal of the rejections, is therefore respectfully requested.

In particular, claim 5 is rejected as being vague and indefinite because, since “ the claim does not indicate the correlation between monitoring the deprotection of the 5’ protecting group and detecting errors in the sequence of the newly synthesized nucleic acid, it is unclear why

errors in the sequence of the newly synthesized nucleic acid can be detected based in results from the step of monitoring.” As is disclosed in paragraphs [0030] and [0136] of the Specification, monitoring the deprotection of the 5’ group is performed to eliminate deletion errors. In the embodiment of claim 5, the growing strand is deprotected, and the result is monitored, in one embodiment (claimed in claim 11) by flowing the wash through a nanopore and determining whether fluorescence is detected. If not, the steps are constantly repeated until it is determined that no more deletion errors are present, in one embodiment by detection of fluorescence in the wash. The Applicants further note that methods and materials related to the use of nanopore devices are well-known in the art, being discussed in many of the references disclosed by the Applicants in the Information Disclosure Statement submitted in this case, including, but not limited to, Deamer, D.W., Branton, D., *Characterization of Nucleic Acids by Nanopore Analysis I*, ACC. CHEM. RES., Vol. 35, No. 10, 817-825 (2002), which was incorporated by reference into the present application. The Applicants therefore respectfully submit that the meaning of claim 5 is perfectly clear and definite, as it is clear that the synthesized nucleic acid is deprotected and the deprotection process is monitored in order to determine when no sequence errors remain in the synthesized nucleic acid.

Furthermore, in order to more particularly point out and claim the invention, the Applicants have herein amended claim 5 to recite the steps of eliminating deletion errors in the sequence of the synthesized nucleic acid by the step of monitoring the deprotection of the 5’ protecting group and repeating steps a) and b) until all deletion errors in the sequence of the synthesized nucleic acid are eliminated. Claim 14 has been similarly amended. Support for these amendments is found in the Specification at least at paragraphs [0030] and [0136], and in Fig. 14B. No new matter is added by these amendments. Entry of the amendments and withdrawal of the rejection of claim 5, as amended, is therefore respectfully requested.

Claim 12 is rejected as being vague and indefinite because “it is unclear why change in electrophoretic force can be exerted by the newly synthesized nucleic acid as it grows.” As discussed in the previous section, and disclosed in the Specification, the embodiment claimed in claim 12 makes use of a magnetic (or optical) tweezer. The addition of an oligonucleotide strand creates an increase in electrophoretic force felt by the support, as is well known, which increased electrophoretic force moves the support from its equilibrium position and necessitates increasing the magnetic field gradient in order to restore the support to the equilibrium position. The restoration force may then be used to determine the number of bases added. The Applicants

therefore respectfully submit that the limitation of claim 12 is neither vague nor indefinite, being fully disclosed and supported in the Specification.

Furthermore, in order to clarify that the electrophoretic force created by the growing nucleic acid is exerted on the support, the Applicants have herein amended claim 12 to recite that the step of detecting a change in electrophoretic force detects a “change in the electrophoretic force exerted by the synthesized nucleic acid on the solid support as it grows”. Claim 15 has been similarly amended. Support for these amendments is found in the Specification at least at paragraphs [0022], [0118]-[0120], and [0137]-[0143], and in Figs. 11A-G. No new matter is added by these amendments. Entry of the amendments and withdrawal of the rejection of claim 12, as amended, is therefore respectfully requested.

Claims 13 and 16 are rejected as being vague and indefinite because “it is unclear that a plurality of what reactions are carried out in parallel using a plurality of light sources and detectors.” The Applicants have herein amended claims 13 and 16 to clarify the claim language by reciting that the term “reaction” refers to the process steps of the underlying base claim. Hence, claim 13 is amended to recite “a plurality of reactions comprising steps (a)-(c)” and claim 16 is amended to recite “a plurality of reactions comprising steps (a)-(e)”. Support for these amendments is found in the Specification at least at paragraphs [0026]-[0027] and [0125]-[0130], and [0135], in Figs. 11A and B and 12 A and B, and in original claim 7. No new matter is added by this amendment. Entry of the amendment and withdrawal of the rejections of claims 13 and 16, as amended, is therefore respectfully requested.

IV. Rejections under 35 U.S.C. 102(e)

Claims 4 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Gascoyne. The Applicants respectfully traverse the rejections, on the grounds that any rejection over Gascoyne is improper, because the filing date of Gascoyne is too late for Gascoyne to be available for use as prior art against the present application. The filing date of the Gascoyne application is January 3, 2003. The instant application was filed December 10, 2003 and claims the benefit under 35 U.S.C. 119(e) of U.S. Prov. App. Ser. No. 60/432,556 (“the ‘556 provisional”), filed December 10, 2002. The Applicants respectfully note that the Applicants’ claim for the benefit of the ‘556 provisional is reflected in the Application Data presented on the USPTO website and that the Applicants’ Specification contains the required language referring to the earlier application.

The prior art provisions of 35 U.S.C. 102(e), as laid out in the Office Action, require that the invention be described in a an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent. By virtue of the claim for benefit to the '556 provisional application, which was filed on December 10, 2002, the effective cutoff filing date for the availability of a published application for use as prior art against the present application is therefore December 9, 2002 (the "critical date"). The filing date of Gascoyne, January 3, 2003, is after the critical date of December 9, 2002. The Gascoyne reference is therefore not available for use as prior art against the present application. Reconsideration and withdrawal of the rejections of claims 4 and 17 under 35 U.S.C. 102(e) over Gascoyne is therefore respectfully requested.

With the Gascoyne reference being unavailable, the art of record fails to anticipate or make obvious the Applicants' invention, whether taken alone or in combination. Allowance of claims 4 and 17 is therefore respectfully requested.

V. Rejections under 35 U.S.C. 103(a)

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gascoyne in view of White. The Applicants respectfully traverse the rejection. As discussed in the previous section, any rejection over Gascoyne is improper, because the filing date of Gascoyne is too late for Gascoyne to be available for use as prior art against the present application. With the Gascoyne reference being unavailable, the art of record fails to anticipate or make obvious the Applicants' invention, whether taken alone or in combination. Reconsideration and withdrawal of the rejection of claim 16 under 35 U.S.C. 103(a) over Gascoyne in view of White is therefore respectfully requested.

VI. Conclusion

Claims 4, 5, and 12-18 have been amended. No new matter is presented by these amendments. The Applicants respectfully submit that claims 4, 5, and 11-18 are now in condition for allowance, which action is now requested. For this reason, and in view of the foregoing arguments, the Applicants believe that this application is now in condition for allowance, which action is respectfully solicited. Due to the impending expiration of the extended time for reply, a Request for Continued Examination is being submitted with this response in order to keep the application pending while the Examiner considers the Applicants'

response. Should there remain any unresolved issues, it is respectfully requested that the Examiner telephone Norma E. Henderson, Applicants' Attorney, at 603-437-4400, so that such issues may be resolved as expeditiously as possible.

Respectfully Submitted,



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